PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GEMBICEN 200 mg concentrate for solution for infusion

GEMBICEN 1 000 mg concentrate for solution for infusion

GEMBICEN 2 000 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of concentrate contains gemcitabine hydrochloride equivalent to 38 mg gemcitabine.

GEMBICEN 200 mg: Each 10 ml vial contains 5,26 ml solution and gemcitabine hydrochloride equivalent to 200 mg gemcitabine.

GEMBICEN 1 000 mg: Each 30 ml vial contains 26,3 ml solution and gemcitabine hydrochloride equivalent to 1 000 mg gemcitabine.

GEMBICEN 2 000 mg: Each 100 ml vial contains 52,6 ml solution and gemcitabine hydrochloride equivalent to 2 000 mg gemcitabine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear and colourless to light straw coloured solution.

The pH of the solution is between 2,0 and 3,0.

The osmolality ratio is 270 ± 20 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GEMBICEN is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

GEMBICEN is indicated as first-line treatment for patients with locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. GEMBICEN is indicated for patients previously treated with 5-FU (fluorouracil).
GEMBICEN is indicated for treatment of patients with transitional cell bladder cancer.

GEMBICEN, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
GEMBICEN, alone or in combination, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based chemotherapy.

4.2 Posology and method of administration

Posology:

Patients with hepatic or renal impairment

GEMBICEN should be used with caution in patients with hepatic insufficiency or with impaired renal function as no studies have been done in patients with significant renal or hepatic impairment. There is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

Non-small cell lung cancer

Adults: The recommended mono-chemotherapy dosage is 1 000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one-week

rest period. This four-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

GEMBICEN may be used in combination with cisplatin using either a three-week or a four-week schedule. One of the following regimens is suggested:

3-week schedule: GEMBICEN 1 250 mg/m², given by 30-minute intravenous infusion on days 1 and 8 of every 21 day cycle and cisplatin 100 mg/m² on day 1. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

4 week schedule: GEMBICEN 1 000 mg/m^2 on days 1, 8 and 15 of every
28 day cycle and cisplatin 100 mg/m^2 on either day 1, 2 or 15 of therapy. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Pancreatic cancer

Adults: The recommended dose of GEMBICEN is 1 000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Bladder cancer

Adults: The recommended monochemotherapy dosage of GEMBICEN is 1 250 mg/m², given by 30 minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

GEMBICEN may be used in combination with cisplatin. The recommended dose of GEMBICEN is 1 000 mg/m², given by 30 minute infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day

1 following GEMBICEN or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast cancer

Adults: GEMBICEN in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2) administered on day 1 over approximately 3 hours as an intravenous infusion, followed by GEMBICEN (1 250 mg/m^2) as a 30 minute intravenous infusion on days 1 and 8 of each 21 day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1 500 (x 10^6 /L) prior to initiation of GEMBICEN and paclitaxel combination.

Ovarian cancer

Single medicine use in adults: The recommended dose of GEMBICEN is 800 to 1 250 mg/m^2, given by a 30 minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use in adults: GEMBICEN in combination with carboplatin is recommended using GEMBICEN 1 000 mg/m^2 administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After GEMBICEN, carboplatin will be given on day 1 consistent with a target area under the curve (AUC) of 4,0 g/ml/min. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.
Patients receiving GEMBICEN should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of GEMBICEN may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

Table 2:

Absolute granulocyte count (x 10^6/L)		**Platelet count (x 10^6/L)**	**Percentage of full dose (%)**
> 1 000	and	> 100 000	100
500 – 1 000	or	50 000 – 100 000	75
< 500	or	< 50 000	hold

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Doses should be withheld until toxicity has resolved in the opinion of the medical practitioner. GEMBICEN is well tolerated during the infusion, with only a few cases of injection site reaction reported. GEMBICEN can be easily administered on an outpatient basis.

Special populations

Elderly patients: GEMBICEN has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although GEMBICEN clearance and half-life are affected by age.

Paediatric population

Safety and effectiveness in children have not been established.

Method of administration:

GEMBICEN is for intravenous use only.

GEMBICEN is administered as a 30 minute intravenous infusion.

For instructions on dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

Patients with known hypersensitivity to gemcitabine or to any of the excipients listed in section 6.1.

Pregnancy and breastfeeding: The safety of gemcitabine in human pregnancy and lactation has not been established.

Usage in children: Safety and effectiveness in children have not been established.

4.4 Special warnings and precautions for use

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

Haematological toxicity

GEMBICEN can suppress bone marrow function as manifested by leucopenia, thrombocytopenia and anaemia. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count (see section 4.2 & 4.8)

Patients receiving GEMBICEN should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when medicine-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short-lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after GEMBICEN administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. The risk of cumulative bone-marrow suppression must be considered when GEMBICEN treatment is given together with other chemotherapy.

Hepatic and renal impairment

GEMBICEN should be used with caution in patients with hepatic impairment or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

Administration of GEMBICEN in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic impairment.

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤ 7 days apart): Toxicity has been reported (see section 4.5).

Live vaccinations

Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with GEMBICEN (see section 4.5).

Nervous system

Posterior reversible encephalopathy syndrome

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single treatment or in combination with other chemotherapeutic treatments. Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES, but other symptoms, such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. GEMBICEN should be permanently discontinued and supportive measures implemented, including blood pressure control and antiseizure therapy, if PRES develops during therapy.

Cardiovascular

Due to the risk of cardiac and/or vascular disorders with GEMBICEN, particular caution must be exercised with patients presenting a history of cardiovascular events.

Capillary leak syndrome

Capillary leak syndrome has been reported in patients receiving gemcitabine as single treatment or in combination with other chemotherapeutic treatments (see section 4.8). The condition is usually treatable if recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal impairment and pulmonary oedema.

GEMBICEN should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Pulmonary

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing GEMBICEN therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Haemolytic uraemic syndrome

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were less frequently reported (post-marketing data) in patients receiving gemcitabine (see section 4.8). HUS is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

GEMBICEN contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per unit volume, that is to say it is essentially sodium free.

4.5 Interactions with other medicines and other forms of interaction

No specific interaction studies have been performed (see section 5.2).

Radiotherapy

Concurrent (given together or ≤ 7 days apart) – Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1 000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4 795 cm^3). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2 twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given > 7 days apart) – Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggests that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine, as in GEMBICEN.

Others

Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of GEMBICEN in pregnant women. Studies in animals have shown reproductive toxicity. Based on results from animal studies and the mechanism of action of gemcitabine, GEMBICEN should not be used during pregnancy (see section 4.3). Women should be advised not to become pregnant during treatment with GEMBICEN and to warn their attending medical practitioner immediately, should this occur after all.

Breastfeeding

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breastfeeding must be discontinued during GEMBICEN therapy (see section 4.3).

Fertility

In fertility studies gemcitabine caused hypospermatogenesis in male mice. Therefore, men being treated with GEMBICEN are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with GEMBICEN.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However,

GEMBICEN can cause mild to moderate somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, proteinuria and haematuria, dyspnoea (highest incidence in lung cancer patients), allergic skin rashes which is associated with itching in some patients.

The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions I n thrombocyte, leucocyte and granulocyte counts (see section 4.2).

Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Infections and infestations	Frequent	Infections.
	Frequency unknown	Sepsis.
Blood and lymphatic system disorders	Frequent	Leucopenia (Neutropenia Grade 3 = 19,3 %; Grade 4 = 6 %). Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2 & 4.4), thrombocytopenia, anaemia, febrile neutropenia. Dosage reduction or omission may be

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
		necessary for severe bone marrow depression (see section 4.2).
	Less frequent	Thrombocytosis, thrombotic microangiopathy.
Immune system disorders	Less frequent	Anaphylactoid reaction.
Metabolism and nutrition disorders	Frequent	Anorexia
Nervous system disorders	Frequent	Headache, insomnia, somnolence
	Less frequent	Cerebrovascular accident, posterior reversible encephalopathy syndrome (see section 4.4).
Cardiac disorders	Less frequent	Dysrhythmias (predominantly supraventricular in nature), heart failure, myocardial infarction
Vascular disorders	Less frequent	Clinical signs of peripheral vasculitis and gangrene, hypotension, capillary leak syndrome (see section 4.4).
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea – usually mild and passes rapidly without treatment, cough, rhinitis.
	Less frequent	Interstitial pneumonitis (see section 4.4), bronchospasm – usually mild and transient but may require parenteral treatment, pulmonary oedema, adult respiratory distress syndrome (see section 4.4).

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
	Frequency unknown	Pulmonary eosinophilia.
Gastrointestinal disorders	Frequent	Vomiting, nausea, diarrhoea, stomatitis and ulceration of the mouth, constipation.
	Less frequent	Ischaemic colitis.
Hepatobiliary disorders	Frequent	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, increased bilirubin.
	Less frequent	Serious hepatotoxicity including liver failure and death, increased gamma-glutamyl transferase (GGT).
Skin and subcutaneous tissue disorders	Frequent	Allergic skin rash frequently associated with pruritus, alopecia, itching, sweating.
	Less frequent	Severe skin reactions, including desquamation and bullous skin eruptions, ulceration, vesicle and sore formation, scaling, toxic epidermal necrolysis, Stevens-Johnson syndrome.
	Frequency unknown	Pseudocellulitis.
Musculoskeletal and connective tissue disorders	Frequent	Back pain, myalgia.
Renal and urinary disorders	Frequent	Haematuria, mild proteinuria.
	Less frequent	Renal failure (see section 4.4),

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
		haemolytic uraemic syndrome (see section 4.4).
General disorders and administration site conditions	Frequent	Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia, cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. Oedema/peripheral oedema, including facial oedema. Oedema is usually reversible after stopping treatment. Fever, asthenia, chills.
	Less frequent	Injection site reactions – mainly mild in nature.
Injury, poisoning and procedural complications	Less frequent	Radiation toxicity (see section 4.5), radiation recall.

Description of selected adverse reactions

Combination use in breast cancer

The frequency of grade 3 and 4 haematological toxicities, particularly neutropenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events. Fatigue and febrile neutropenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

Oedema

Oedema is usually reversible after stopping treatment. The mechanism of the toxicity is unknown. It is not associated with any evidence of cardiac, hepatic or renal failure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of
GEMBICEN is important. It allows continued monitoring of the benefit/risk balance of GEMBICEN. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no known antidote for overdose of gemcitabine. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agents/pyrimidine analogues.

ATC code: L01BC05.

Mechanism of action

Cellular metabolism and mechanism of action:

Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for

catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Secondly, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).

Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Cytotoxic activity in cell cultures

Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. In *in vitro* studies, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

Antitumour activity in preclinical models

In animal tumour models, antitumour activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumour activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumour activity against a broad spectrum of mouse tumours.

5.2 Pharmacokinetic properties

Absorption:

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3,2 to 45,5 µg/ml. Plasma concentrations of the parent compound following a dose of 1 000 mg/m^2/30 minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion, and greater than 0,4 µg/ml for an additional hour.

Distribution:

The volume of distribution of the central compartment was 12,4 L/m^2 for women and 17,5 L/m^2 for men (inter-individual variability was 91,9 %). The volume of distribution of the peripheral compartment was 47,4 L/m^2. The volume of the peripheral compartment was not sensitive to gender. The plasma protein binding was considered to be negligible.

Half-life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Biotransformation:

Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono-, di- and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'-deoxy-2', 2'-difluorouridine (dFdU), is not active and is found in plasma and urine.

Elimination:

Systemic clearance ranged from 29,2 L/h/m^2 to 92,2 L/h/m^2 depending on gender and age (inter-individual variability was 52,2 %). Clearance for women is approximately 25 % lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1 000 mg/m^2 given as a 30 minute infusion, lower clearance

values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10 % is excreted as unchanged drug.

Renal clearance was 2 to 7 L/h/m^2. During the week following administration, 92 to 98 % of the dose of gemcitabine administered is recovered, 99 % in the urine, mainly in the form of dFdU and 1 % of the dose is excreted in faeces.

Linearity

The pharmacokinetics of gemcitabine appear to be linear over the doses examined.

dFdCTP kinetics

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35 – 350 mg/m^2/30 minutes, which give steady state concentrations of 0,4 – 5 µg/mL. At gemcitabine plasma concentrations above 5 µg/mL, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.

Half-life of terminal elimination: 0,7 – 12 hours.

dFdU kinetics

Peak plasma concentrations (3 – 15 minutes after end of 30 minute infusion, 1 000 mg/m^2): 28 – 52 µg/mL. Trough concentration following once weekly dosing: 0,07 – 1,12 µg/mL, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half-life of terminal phase 65 hours (range 33 – 84 h).

Formation of dFdU from parent compound: 91 % – 98 %.

Mean volume of distribution of central compartment: 18 L/m^2 (range 11 – 22 L/m^2).

Mean steady state volume of distribution (Vss): 150 L/m^2 (range 96 – 228 L/m^2).

Tissue distribution: Extensive.

Mean apparent clearance: 2,5 L/m^2 (range 1 – 4 L/m^2).

Urinary excretion: All.

Gemcitabine and paclitaxel combination therapy:

Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

Gemcitabine and carboplatin combination therapy:

When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

Renal impairment:

Mild to moderate renal insufficiency (glomerular filtration rate [GFR] from 30 mL/min to 80 mLmin) has no consistent, significant effect on gemcitabine pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines, except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

24 months.

In-use shelf life

After dilution, chemical and physical in-use stability has been demonstrated for:

Table 3:

Diluent	Storage conditions	Time period
0,9 % sodium chloride solution for infusion	2 ºC – 8 ºC in absence of light in non-PVC (polyolefin) infusion bags	84 days
0,9 % sodium chloride solution for infusion	2 ºC – 8 ºC in absence of light in PVC infusion bags	24 hours
0,9 % sodium chloride solution for infusion	25 ºC under normal lighting conditions in PVC infusion bags	24 hours
5 % glucose solution for infusion	25 ºC under normal lighting conditions in PVC infusion bags	24 hours

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at 2 ºC – 8 ºC.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

GEMBICEN 200 mg:

A 10 ml, USP type-I glass vial, stoppered with a grey bromo butyl rubber stopper and sealed with a red coloured aluminium flip-off top.

Each vial contains 5,26 ml concentrate.

GEMBICEN 1 000 mg:

A 30 ml, USP type-I glass vial, stoppered with a grey bromo butyl rubber stopper and sealed with a red coloured aluminium flip-off top.

Each vial contains 26,3 ml concentrate.

GEMBICEN 2 000 mg:

A 100 ml, USP type-I glass vial, stoppered with a grey bromo butyl rubber stopper and sealed with a red coloured aluminium flip-off top.

Each vial contains 52,6 ml concentrate.

Pack size:

1 vial placed in outer carton.

6.6 Special precautions for disposal and other handling

Handling

The normal safety precautions for cytostatic medicines must be observed when preparing and disposing of the infusion solution. Handling of the concentrate should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for the dilution of the solution for injection

The only approved diluent for GEMBICEN is sodium chloride 9 mg/ml (0,9 %) solution for injection (without preservatives):

1. Use the aseptic technique during any dilution of GEMBICEN for intravenous infusion administration.
2. Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

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8. REGISTRATION NUMBERS

GEMBICEN 200 mg: 57/26/0299

GEMBICEN 1 000 mg: 57/26/0300

GEMBICEN 2 000 mg: 57/26/0301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 July 2025

10. DATE OF REVISION OF THE TEXT

To follow